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JOURNAL SCAN

SUMMARY OF KEY ARTICLES

Immune Response Modifier Therapy in Anogenital Warts and Actinic Keratoses

INTRODUCTION BY THOMAS J. ZUBER, MD, MPH, MBA

Journal of the American Academy of Dermatology	Carrasco D, vander Straten M, Tyring SK. Treatment of anogenital warts with imiquimod 5% cream followed by surgical excision of residual lesions. *J Am Acad Dermatol.* 2002;47(4 suppl):S212-S216.
Archives of Gynecology and Obstetrics	Haidopoulos D, Diakomanolis E, Rodolakis A, Vlachos G, Elsheikh A, Michalas S. Safety and efficacy of locally applied imiquimod cream 5% for the treatment of condylomata acuminata of the vulva. *Arch Gynecol Obstet.* 2004;270:240-243.
Sexually Transmitted Diseases	Sauder DN, Skinner RB, Fox TL, Owens ML. Topical imiquimod 5% cream as an effective treatment for external genital and perianal warts in different patient populations. *Sex Transm Dis.* 2003;30:124-128.
Journal of the American Academy of Dermatology	Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: Results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol.* 2004;50:714-721.
Dermatologic Surgery	Lee PK, Harwell WB, Loven KH, et al. Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. *Dermatol Surg.* 2005;31:659-664.
Current Therapeutic Research	Tyring SK. Immune-response modifiers: A new paradigm in the treatment of human papillomavirus. *Curr Ther Res.* 2000;61:584-596.

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INTRODUCTION

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Actinic keratoses (AKs) and external anogenital warts are two of the most common skin disorders encountered in general office practice. Historically, these lesions have been treated with a variety of surgical ablative procedures, including cryotherapy and electrocautery. More recently, the concept of field therapy has emerged in treating dermatologic diseases that tend to occur over a wide area of the skin. AKs and external anogenital warts appear to be regional diseases; treatment of a single lesion or a single anatomic site may fail to prevent future disease in nearby tissues.

The introduction of imiquimod has redefined field therapy. Imiquimod is an immune response modifier (IRM) that has been used for nearly a decade in the treatment of anogenital warts. In 2004, the US Food and Drug Administration approved imiquimod for the treatment of AKs of the face and scalp and superficial basal cell carcinomas. Adding a medication such as imiquimod to the practitioner's armamentarium may provide greater patient benefit over historically used surgical procedures.

As Tyring[1] explains, imiquimod upregulates the immune system, changing the body's response to certain cutaneous insults—ultraviolet (UV) light damage in the case of AKs, and human papillomavirus (HPV) infection in the case of anogenital warts. IRM medications have demonstrated safe antiviral and antitumor activity with limited side effects and ease of application.

The experience with field therapy for AKs, in particular, has been well described and illustrates the utility of this strategy. The goal of treating a wide area of sun-damaged skin is to eliminate both visible lesions and subclinical AKs, reducing or eliminating the emergence of additional visible lesions within the same anatomic field.

AKs are recognized as being on the same continuum with invasive squamous cell carcinomas (SCCs). UV light exposure has been shown to cause both genetic damage in keratinocytes as well as local immunosuppression; both are found in sun-damaged skin and are recognized factors in the development of AKs and SCCs.[2,3]

Not all AKs evolve along this continuum to become SCCs, but an estimated 10% of AKs progress to SCC within 10 years.[4] Further, histologic evidence of adjacent AKs may be found in as many as 97.2% of cases of SCCs.[3] Both AKs and SCCs are characterized by keratinocytic atypia and differ only in the depth of their presence in the skin—whereas AKs are partial-thickness lesions confined to the epidermis, invasive SCCs extend into the dermis.

Tyring[1] notes that the mechanism by which imiquimod works in AKs—enhancement of the immune response—also functions to reduce the HPV load in the local area of visible condylomata. This reduction in viral load is thought to be the means by which imiquimod therapy reduces condyloma recurrence.

Family physicians are in a unique, frontline position to identify and treat patients with anogenital warts and AKs. This supplement includes summaries of six articles that review imiquimod's mechanism of action and the results of clinical trials examining the use of imiquimod in patients with anogenital warts and AKs. The IRMs have the ability to change the local immune milieu, and future medications in this class may be able to enhance immune suppression of internal diseases. ■

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Condyloma Recurrence Rates Improve With Immune Response Modifier Treatment

Imiquimod Plus Surgical Excision May Improve Long-Term Outcome

Recurrence of anogenital warts can result from reinfection with human papillomavirus (HPV) following successful therapy or from emergence of lesions resulting from HPV remaining in apparently normal skin. Since locally destructive treatment modalities eliminate lesions but have no effect on HPV infection, recurrence has been a particularly common problem in patients treated with techniques such as cryotherapy and surgical excision.

Carrasco and coworkers conducted a retrospective study to determine whether imiquimod treatment followed by surgical excision of any residual lesions would reduce the long-term recurrence rates of anogenital warts.

Study Design and Population

The authors examined the charts of 60 patients who had experienced a treatment failure with at least one method other than imiquimod and who had been treated with imiquimod for genital warts either every night or three nights per week for up to 16 weeks. The patients were given the option to have surgical excision of any warts that remained after the completion of imiquimod therapy.

The patients' charts were divided into three groups with 20 charts per group: (1) complete clearance with imiquimod monotherapy, (2) partial response to 16 weeks of imiquimod therapy followed by surgical excision of residual lesions, and (3) use of 16 weeks of placebo followed by surgical excision of residual warts, or surgical excision alone without prior use of placebo or imiquimod. The follow-up period ranged from 2 to 7 years (mean, 5.7 years).

Clinical Results

Among the patients who had surgical excision alone, the recurrence rate was 65% (in 13 patients), with an average time to recurrence of 5 months (**Table**). Four patients (20%) who had imiquimod followed by surgical excision of residual lesions experienced recurrence of disease within an average of 19 months. Three of the patients (15%) who were treated with imiquimod monotherapy experienced recurrence of warts within an average of 17 months.

Conclusion

This small retrospective study presents the hypothesis that sequential treatment of imiquimod followed by surgical excision may be a viable intervention, yielding long-term clearance, for patients who do not achieve complete clearance of anogenital warts with imiquimod monotherapy. The investigators suggest that this hypothesis be tested in controlled prospective trials using imiquimod before or after surgical excision of condylomata. ■

Table. Recurrence Rates of Anogenital Warts Following Complete Clearance With Three Different Forms of Therapy

Therapy	Recurrence Number (Rate)	Average Time to Recurrence
Surgical excision	13 (65%)	5 months
Imiquimod monotherapy	3 (15%)	17 months
Imiquimod + surgical excision of residual warts	4 (20%)	19 months

Source: Adapted from Carrasco D, vander Straten M, Tyring SK. Treatment of anogenital warts with imiquimod 5% cream followed by surgical excision of residual lesions. *J Am Acad Dermatol.* 2002;47(4 suppl):S212-S216.

Based on Carrasco D, vander Straten M, Tyring SK. Treatment of anogenital warts with imiquimod 5% cream followed by surgical excision of residual lesions. *J Am Acad Dermatol.* 2002;47(4 suppl):S212-S216.

3-Year Experience With Imiquimod in Vulvar Warts

Reduced Recurrence of Vulvar Warts Possible

The conventional methods of treating condylomata acuminata are surgery, cryotherapy, electrodesiccation, and physician-applied topical agents (including trichloroacetic acid). The introduction of podophyllin and imiquimod provided the opportunity for patients to manage their own treatment.

Imiquimod was approved by the US Food and Drug Administration in 1997 for the treatment of anogenital warts. Since that time, clinical investigators have conducted studies of the safety and efficacy of this therapy in various patient populations. Haidopoulos and colleagues conducted a study of imiquimod's use to treat vulvar warts in a group of patients at a hospital in Athens, Greece.

Study Design and Population

Over a period of 3 years, the investigators enrolled 73 women with condylomata of the vulva who had been referred to the hospital's colposcopy unit. There were two requirements for inclusion: no treatment of any kind in the 6 weeks prior to being seen at the clinic, and no lesions in the vulvar area other than condylomata acuminata. Patients who had precancerous conditions or malignancy in the genital area were excluded from the study. Also excluded for medical rea-

sons were patients with very large condylomata, as well as patients who were immunosuppressed or pregnant, all of whom were treated with laser carbon dioxide vaporization.

The 73 patients were instructed to cleanse the treatment area and then apply imiquimod 5% cream to the area of visible warts three times weekly at bedtime. They were told to wash the area with water in the morning. Treatment applications continued for 12 weeks, and patients were seen every 4 weeks during this time. At each visit, the investigators assessed the patients for clearance of the lesions and documented patient reports of systemic or local adverse effects.

At the end of 12 weeks, patients who had not experienced at least partial clearance of warts were treated with laser carbon dioxide vaporization. Those who had total clearance during the 12-week treatment period or total or partial clearance at the end of the treatment period were enrolled in a 3-month follow-up protocol.

Clinical Results

A total of 62 patients completed the study (**Table**); 11 dropped out for personal reasons unrelated to therapy and were not counted as treatment failures. Four of the 62 patients had no improvement and were considered treatment failures.

Table. Response to Therapy

Response	Number of Patients	Percentage
Complete	44/62	71%
Partial (>50% reduction of size)	53/62	85%
Partial (<50% reduction of size)	5/62	8%
None (treatment failures)	4/62	6%

Source: Haidopoulos D, Diakomanolis E, Rodolakis A, Vlachos G, Elsheikh A, Michalas S. Safety and efficacy of locally applied imiquimod cream 5% for the treatment of condylomata acuminata of the vulva. *Arch Gynecol Obstet.* 2004;270:240-243. Used with permission of Springer Science and Business Media.

Forty-four of the remaining 58 patients had total clearance; 53 experienced a reduction in lesion size of 50% or more; 5 had less than 50% clearance. The investigators point out that 19 patients (43%) of those who had complete resolution achieved clearance within the first 6 weeks of treatment.

Seventeen patients were lost to follow-up during the 3-month posttherapy protocol. Of the remaining 45 patients, 6 (13%) experienced a recurrence of warts—in all cases, more than one lesion. These new lesions were treated with laser carbon dioxide vaporization. The rest of the patients remained disease-free for the duration of the 3-month follow-up period.

The most common side effect of therapy was erythema, reported by 28 (45%) patients. Five of these patients reported severe erythema; they were instructed to stop using imiquimod for 2 weeks, then resume applications for a total of 12 weeks of therapy. Four of these patients had complete clearance and one had less than 50% partial clearance.

Conclusion

This open-label study had a small sample size, and patients with severe disease (giant condylomata) were excluded. Nevertheless, 85% of the patients achieved at least 50% clearance of vulvar warts, and 71% of the participants had complete clearance. Thirteen percent of the women who had either complete or partial clearance experienced a recurrence of warts within the 3-month follow-up period. The researchers quote statistics from other studies that report rates of recurrence with conventional methods of treatment ranging from 25% to 60% (with local agents) to 15% to 80% (with surgical treatments). The authors suggest that further study is warranted in immunosuppressed patients and those with severe disease. ■

Based on Haidopoulos D, Diakomanolis E, Rodolakis A, Vlachos G, Elsheikh A, Michalas S. Safety and efficacy of locally applied imiquimod cream 5% for the treatment of condylomata acuminata of the vulva. *Arch Gynecol Obstet.* 2004;270:240-243.

Placebo-Controlled Trial in External Anogenital Warts

Imiquimod Efficacy Unaffected by Patient Variables

The effectiveness of topical 5% imiquimod cream in treating external genital and perianal condylomata acuminata has been clearly demonstrated in trials, and the medication has a long track record of efficacy in clinical use. Because the possible differential efficacy in anogenital warts in different patient populations had not been documented, Sauder and colleagues conducted an analysis of data from an efficacy study to determine whether demographic variables affect patients' response to imiquimod treatment.

In a previously published study, Edwards and coworkers (*Arch Dermatol.* 1998;134:25-30) reported the results of a vehicle-controlled study of imiquimod vs vehicle. An intent-to-treat analysis showed that 54 of 109 patients treated with imiquimod (50%) had clearance of anogenital warts; clearance was demonstrated in 11 of 100 patients (11%) in the control group ($P < 0.0001$). Sauder and colleagues examined the clearance rates in subgroups of patients who received

either imiquimod or vehicle alone. The subgroups were determined according to the variables listed in **Table 1**.

Table 1. Demographics of Patient Subgroups

Gender	Age
Baseline wart area (mm^2)	Height
Duration of current warts (mo)	Weight
Previous wart treatment (no/yes)	Race (white, black, Asian/Pacific Islander)
Current tobacco use (no/yes)	

Source: Sauder DN, Skinner RB, Fox TL, Owens ML. Topical imiquimod 5% cream as an effective treatment for external genital and perianal warts in different patient populations. *Sex Transm Dis.* 2003;30:124-128.

Study Design and Population

Enrolled in the study were 209 patients with between 2 and 50 warts; 109 were randomized to receive imiquimod 5% cream and 100 to receive vehicle cream only. At the baseline clinic visit, the investigators measured and photographed the warts targeted for treatment.

The patients were instructed to use the imiquimod or vehicle cream three times a week during sleeping time (8 ± 2 hours); the study duration was 16 weeks. Visits to the clinic were scheduled for the end of weeks 1 and 2, then at the end of weeks 4, 6, 8, 10, 12, 14, and 16. The patients' target warts were measured and photographed at each visit. The researchers also documented adverse reactions, including local skin reactions.

Clinical Results

The study group comprised 86 women and 123 men, representing 41% and 59% of patients, respectively. In the women, most of the warts were on the vulva and perianal area; in men, most of the warts were on the penis. The analysis showed that imiquimod efficacy was significantly greater than that of vehicle regardless of gender ($P < 0.0001$). However, women had a higher rate of clearance, 72%; the clearance rate in men was 33%.

The investigators proposed that the difference in clearance rate between women and men may be explained by the nature of the skin in the affected areas. The skin on the shaft of the penis is more keratinized than that on the vulva, which may have had an effect on imiquimod's penetration and efficacy.

Imiquimod also was more effective in clearing both large and small condylomata than was vehicle, but the difference in clearance rates was highest among patients with the largest wart areas (>162 mm^2). In this analysis, however, there was no substantial difference in clearance rates between the subgroup of patients with large warts vs those with smaller warts (50% vs 59%, respectively).

Regarding duration of the current outbreak of warts, imiquimod was significantly more effective than was vehicle regardless of duration ($P < 0.0001$). Among the patients with warts of greater than 6 months' duration, those who received imiquimod had a significantly greater rate of clearance than did those who used vehicle (40% vs 4%, respectively). In the subgroup who had warts for 6 months or less, imiquimod use resulted a clearance rate of 58%, compared to a 17% clearance rate in those in the vehicle group. The relative benefit (imiquimod clearance rate divided by vehicle clearance rate) in the group who had warts for 6 months or less was 3.3; a relative benefit of 9.6 was calculated for the patients whose warts were present for more than 6 months. The authors suggest that this great difference can be accounted for by the low clearance rate in the subgroup of patients with long-standing disease who were assigned to the vehicle group.

A significant difference was found between imiquimod and vehicle in the patients who had been treated previously with a variety of physician-applied treatments as well as patient-applied podophyllotoxin ($P < 0.05$). Imiquimod also was significantly more effective than was vehicle in clearing condylomata in patients who had not been treated for their current disease outbreak ($P < 0.05$).

These clinical results, as well as the data on the other variables analyzed, are summarized in **Table 2**.

Table 2. Relative Benefit of Imiquimod Compared to Vehicle in Patient Subgroups

		Complete Clearance Rates: Number of Recipients		
Variable	Subgroup	Imiquimod 5%	Vehicle	Relative Benefit*
Gender	Female	72% (33/46)	20% (8/40)	3.6
	Male	33% (21/63)	5% (3/60)	6.7
Baseline wart area	<34 mm^2	59% (16/27)	13% (3/24)	4.7
	34-75 mm^2	48% (14/29)	18% (4/22)	2.7
	75-162 mm^2	40% (10/25)	14% (4/29)	2.9
	>162 mm^2	50% (14/28)	0% (0/25)	Infinity
Length of current outbreak	≤6 months	58% (34/59)	17% (9/52)	3.3
	>6 months	40% (20/50)	4% (2/48)	9.6
Previous wart treatments	No	47% (18/38)	10% (3/30)	4.7
	Yes	51% (36/71)	11% (8/70)	4.4
Current tobacco use	No	44% (23/52)	13% (7/52)	3.3
	Yes	54% (31/57)	8% (4/48)	6.5

*Relative benefit = Imiquimod clearance rate divided by vehicle clearance rate.

Source: Adapted from Sauder DN, Skinner RB, Fox TL, Owens ML. Topical imiquimod 5% cream as an effective treatment for external genital and perianal warts in different patient populations. *Sex Transm Dis.* 2003;30:124-128. Used with permission.

Conclusion

The study published by Edwards and colleagues demonstrated that imiquimod is significantly better than is vehicle in clearing anogenital warts in immunocompetent patients. The analysis by Sauder and coworkers discussed here showed that imiquimod's superior efficacy over vehicle remained significant regardless of the patient variables examined. ■

Based on Sauder DN, Skinner RB, Fox TL, Owens ML. Topical imiquimod 5% cream as an effective treatment for external genital and perianal warts in different patient populations. *Sex Transm Dis.* 2003;30:124-128.

Phase III Trials of Imiquimod in Actinic Keratosis

Efficacy and Safety of Immune Response Modifier Treatment Demonstrated

In 1997, the US Food and Drug Administration (FDA) approved imiquimod 5% cream for the treatment of anogenital warts. Its mechanism of action—induction of cytokines and other crucial elements of the immune system—prompted researchers to test imiquimod's potential utility for a variety of other skin diseases. The findings in case reports and pilot studies of this drug's use in patients with actinic keratosis (AK) led to larger, controlled trials, ultimately resulting in the FDA approval of imiquimod for the treatment of AKs. Two of the four phase III clinical trials were conducted by Lebwohl and colleagues.

Study Design and Population

In these two randomized, double-blind, parallel-group, vehicle-controlled studies, imiquimod 5% cream was compared with vehicle alone on clinically diagnosed AKs. The study population consisted of 436 adults who had between four and eight AKs within an area no larger than 25 cm^2 on either the face or the balding scalp. The participants were enrolled at 24 sites in the United States and Canada.

The following were excluded from the study: individuals who had had prior treatment with imiquimod in the treatment area, those with known allergies to any excipients in imiquimod cream or vehicle, and those who had prior treatment with psoralen plus ultraviolet A, ultraviolet B, laser abrasion, dermabrasion, or chemical peel within the previous 6 months. During the study, participants were not permitted to use moisturizers, over-the-counter products containing retinol, or products containing hydroxy acids. Also prohibited during the study, as well as during the 4 weeks prior to starting the study treatment, were topical prescription retinoids, 5-fluorouracil, photodynamic therapy, destruction of lesions with a variety of modalities, and a number of other products and procedures used to treat AK.

After a prestudy period, during which participants were evaluated for eligibility and underwent clinical laboratory testing and physical examination, the subjects who were enrolled were randomized to receive either the study medication or a vehicle cream. The participants were instructed to apply the cream one time on 2 days each week (at least 3 days apart) for 16 weeks. An 8-week follow-up period completed the protocol. Efficacy was assessed at 10 visits, at weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24.

The primary efficacy end point was the rate of complete clearance, which the investigators defined as the proportion of participants who had no clinically visible AKs at week 24 (the end of the 8-week follow-up period). The secondary end point was a 75% or greater reduction over baseline in the AK lesion count (partial clearance) at week 24.

Clinical Results

The rate of complete clearance in the active treatment group was 45.1% and 3.2% in the vehicle-only group ($P < 0.001$) (**Table**). The rate of partial clearance (≥75%) was 59.1% in the active treatment group and 11.8% in the vehicle-only group ($P < 0.001$). The median AK lesion reduction from baseline was 83.3% in the imiquimod group and 0% in the vehicle-only group.

One hundred sixty-six patients (77.2%) in the imiquimod group and 141 of those in the vehicle-only group (63.8%) reported adverse events. Most of these were local skin reactions. Severe erythema was seen in 17.7% of patients in the imiquimod group and 2.3% of those in the vehicle-only group. The investigators state that, overall, imiquimod was well tolerated.

Table. Clearance of AKs With Imiquimod vs Vehicle-Only in Two Phase III Studies

	Imiquimod	Vehicle	*P* Value (95% CI)
COMPLETE CLEARANCE			
Number	97/215	7/221	
			P < 0.001 (34.9%–49%)
Rate	45.1%	3.2%	
PARTIAL CLEARANCE			
Number	127/215	26/221	
			P < 0.001 (39.5%–55.1%)
Rate	59.1%	11.8%	

AK = actinic keratosis; CI = confidence interval.

Source: Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: Results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol.* 2004;50:714-721.

Conclusion

In these two phase III studies, imiquimod 5% cream was shown to be safe and effective in the treatment of AK and provided the added benefit of being patient applied. ■

Based on Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: Results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol.* 2004;50:714-721.

Observational Long-Term Study of Imiquimod in Actinic Keratosis

18 Months of Follow-Up Show Safety and Efficacy

Four phase III studies of imiquimod 5% cream in the treatment of actinic keratoses (AKs) have been conducted, and the medication was approved by the US Food and Drug Administration for this indication in 2004. Imiquimod's mechanism of action includes the upregulation of cytokine responses and the development of local immune memory against actinically damaged keratinocytes. This immune memory has been thought to possibly decrease the incidence of recurrent AKs and prevent the emergence of new lesions, potentially leading also to a decrease in the rate of development of squamous cell carcinomas in the treated fields.

Lee and colleagues conducted an observational study to determine the long-term benefits of imiquimod treatment, to identify any changes that may have occurred to skin quality following the ends of the phase III study periods, and to evaluate the long-term safety of this therapy. Follow-up data ranging from 12 to 18 months (median, 16 months) were included in this evaluation.

The dosage regimens used were once-daily applications twice per week (two studies) and once-daily applications three times per week for 16 weeks (two studies). The anatomic areas treated were the face or balding scalp. The phase III studies showed that both regimens were safe and effective.

Study Design and Population

A total of 146 patients from 30 study centers in which three or more subjects achieved complete (100%) clearance of AKs were included in this study. The original treatment assignments (active or vehicle groups) were not revealed to either the investigators or the patients who participated in the follow-up observational study. One hundred thirty-one patients who had undergone active treatment and 15 of those who had been assigned to the vehicle groups were enrolled in and completed the study.

The rate of recurrence of AKs was the primary variable, which was defined as: (1) the presence at the follow-up visit of at least one AK in the original treatment area or (2) therapy for a skin condition (including one or more AKs) in the treatment area.

Clinical Results

By the end of the study—after a median follow-up of 16 months—19 of the 77 patients (24%) who had used the thrice-weekly regimen had recurrences. Recurrences were reported in 23 of the 54 patients (42.6%) who were in the studies in which the twice-weekly regimen was tested. The **Table** quantifies AK lesion counts for patients with recurrences.

Table. AK Lesion Counts for Patients With Recurrences

Follow-Up AK Lesion Count	Imiquimod 2X/week (n = 19)	Imiquimod 3X/week (n = 16)
1	10 (52.6%)	10 (62.5%)
2	5 (26.3%)	3 (18.8%)
3	3 (15.8%)	2 (12.5%)
4	1 (5.3%)	0 (0.0%)
5	0 (0.0%)	1 (6.3%)
Median	1.0	1.0
Minimum	1.0	1.0
Maximum	4.0	5.0

AK = actinic keratosis.
Four patients in the 2X/week group and three patients in the 3X/week group received treatment for a skin condition that occurred in the treatment area since the previous study and had a follow-up AK lesion count of zero. Data on these patients are not included in this table.

Source: Lee PK, Harwell WB, Loven KH, et al. Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. *Dermatol Surg.* 2005;31:659-664. Used with permission.

The investigators reported that no long-term adverse changes were seen in skin quality among the patients treated with imiquimod. In addition, no long-term safety issues were observed. Patients in both the imiquimod and the vehicle groups had local skin reactions at the follow-up visit; most of these were mild. Four patients who had been treated with imiquimod had local skin reactions that were classified as moderate. However, these reactions were judged to be not clinically meaningful.

Conclusion

Imiquimod acts on the underlying cause of AKs, which likely accounts for the long-term efficacy seen in this study. The investigators emphasize that their reported results are preliminary and that other studies should be done to confirm these findings. ■

Based on Lee PK, Harwell WB, Loven KH, et al. Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. *Dermatol Surg.* 2005;31:659-664.

Immune Response Modifier Mechanism of Action

Imiquimod Induces Immune System to Resist Human Papillomavirus Expression

The ability of the human body to resist and eliminate pathogens depends on an adequate immune response—either innate (nonspecific) or acquired (specific) immunity. The nonspecific response to a challenge by infectious agents is provided by the mechanical barrier of the skin and cellular defenses by neutrophils and macrophages. Two types of acquired responses have been described: humoral and cellular immunity. In the former, B lymphocytes produce immunoglobulins that bind to invading antigens, tagging them for destruction by other mechanisms. When cellular immunity is invoked, specialized cells are produced that react with foreign antigens. Infected cells with viral proteins on their surfaces are identified and killed by the reacting cells. Another way reacting cells can work is by inducing the production of macrophages, which then destroy foreign microorganisms.

Tyring meticulously and clearly explains the complex operations of the myriad components of the immune system. The role of the immune system, and its enhancement by the immune response modifier (IRM) imiquimod, specifically relating to human papillomavirus (HPV) is the main focus of Tyring's review.

The Immune System and External Anogenital Warts

HPV infection prompts the immune system to respond, but it has been demonstrated that this response is slow and not adequate to eliminate virus-infected cells. The partial immune response accounts for the spontaneous regression of condylomata that is seen in 10% to 30% of patients. In the rest, traditional treatment options have comprised a variety of lesion-destructive methods, including surgical excision, cryotherapy, podophyllotoxin, and trichloroacetic acid. However, these modalities have several important limitations: they are associated with patient discomfort, the need for application by a clinician, a high recurrence rate, and the likelihood of latent HPV infection on the skin in the treated area.

IRM treatment represents an important advance because it answers these unmet needs. Imiquimod is applied by patients and its use is not painful; the most common adverse events are local inflammatory reactions at the treatment site, which may be severe in some cases but are usually mild to moderate.

In addition, because imiquimod works by enhancing the immune system to eliminate the HPV viral load, the risks for recurrence and latent infection are reduced. Imiquimod is not directly antiviral, but it stimulates the induction of a number of cytokines (**Table**), which, in turn, activate the immune system, especially cellular immunity.

Table. Summary of the Actions of Certain Cytokines Induced by Imiquimod

Cytokine	Action	Clinical Effect
Interferons	Antiproliferative	Reduction in cell growth
	Antiangiogenic	Reduction of blood vessel growth into tumor
	Antiviral	Stimulation of antiviral cellular immune response
	Enhanced immune recognition	Increased presentation of antigens on cell surface
	Activation of killer cells	Destruction of virus-infected and tumor cells
Interleukins	Attraction of neutrophils	Phagocytosis of tumor and virus-infected cells
	Immunomodulation	Enhanced T_H1 and CTL immunity
Tumor necrosis factor	Local inflammation	Attraction of cells involved in inflammatory response

CTL = cytotoxic T lymphocyte; T_H1 = T-helper cell type 1.

Source: Tyring SK. Immune-response modifiers: A new paradigm in the treatment of human papillomavirus. *Curr Ther Res.* 2000;61:584-596. Used with permission.

Conclusion

The strategy and utility of IRM therapy have yet to be completely explored and defined. At this point, it is clear that the IRM imiquimod stimulates the production of important cytokines in the immune system, and it appears that these cytokines act in a complex way to induce antiviral and antitumor activity. Because of its mechanism of action, IRM treatment may prove beneficial in a number of cutaneous viral and neoplastic diseases. ■

Based on Tyring SK. Immune-response modifiers: A new paradigm in the treatment of human papillomavirus. *Curr Ther Res.* 2000;61:584-596.